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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/812,619	03/30/2004	Po-Ying Chan-Hui	131.02US	3231
33603	7590	04/02/2007	EXAMINER	
MONOGRAM BIOSCIENCES 345 OYSTER POINT BLVD SOUTH SAN FRANCISCO, CA 94080			HALVORSON, MARK	
		ART UNIT	PAPER NUMBER	
		1642		
SHORTENED STATUTORY PERIOD OF RESPONSE		MAIL DATE	DELIVERY MODE	
3 MONTHS		04/02/2007	PAPER	

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	10/812,619	CHAN-HUI ET AL.	
	<b>Examiner</b>	<b>Art Unit</b>	
	Mark Halvorson	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) Responsive to communication(s) filed on 05 January 2007.  
 2a) This action is **FINAL**.                  2b) This action is non-final.  
 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) Claim(s) 1,9,10,12 and 21-26 is/are pending in the application.  
 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.  
 5) Claim(s) \_\_\_\_\_ is/are allowed.  
 6) Claim(s) 1,9,10,12 and 21-26 is/are rejected.  
 7) Claim(s) \_\_\_\_\_ is/are objected to.  
 8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) The specification is objected to by the Examiner.  
 10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.  
     Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
     Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).  
 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
 a) All    b) Some \* c) None of:  
 1. Certified copies of the priority documents have been received.  
 2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)          | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)          | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____. _____   | 6) <input type="checkbox"/> Other: _____                          |

Art Unit: 1642

## **DETAILED ACTION**

Claims 1, 9, 10, 12, 21-26 are pending.

Claims 1, 9, 10, 12, 21-26 are under currently under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

### ***35 USC § 112 1<sup>st</sup> paragraph enablement rejection withdrawn***

The rejection of claims 10 and 25 for failing to comply with the enablement requirement is withdrawn in view of Applicants arguments and the full enablement rejection under 35 USC § 112 1<sup>st</sup> paragraph below.

### ***35 USC § 112 1<sup>st</sup> paragraph written description rejection on binding compounds maintained***

The rejection of claims 12, 21-26 for failing to comply with the written description requirement is maintained.

Applicants argue that numerous examples of binding compounds, including "an antibody binding composition, an antibody, a peptide, a peptide or non-peptide ligand for a cell surface receptor, a protein, an oligonucleotide, an oligonucleotide analog, such as a peptide nucleic acid, [or] a lectin." Applicants argue that at least four different isoforms of VEGF are known. Applicants state that a binding compound can be any "molecular entity capable of specific binding or stable complex formation with an analyte of interest." Applicants further argue that lectins can be used as suitable binding compounds, and refer to Vaisman et al as evidence of lectins binding to VEGF.

Applicant's arguments have been fully considered but they are not persuasive. Applicants state that the genus of binding agents include antibodies, a peptides, non-peptide ligands for a cell surface receptor, an oligonucleotides, and lectins. (page 6, 3<sup>rd</sup> paragraph). This genus includes an enormous number of molecules, of which only a few have been adequately described in the specification, antibodies to the VEGF

Art Unit: 1642

receptor and the VEGF ligands. In addition, lectins bind to glycosylated proteins and would not bind specifically to VEGF receptors. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, applicant was not in possession of the claimed genus.

***35 USC § 112 1<sup>st</sup> paragraph written description rejection on cleavage-inducing moieties withdrawn***

The rejection of claims 12, 21-26 for failing to comply with the written description requirement on cleavage-inducing moieties is withdrawn in view of Applicants arguments.

***35 USC § 102(e) rejections withdrawn***

The rejection of claims 1 and 9 under 35 U.S.C. 102(e) as being anticipated by Klagsbrun et al is withdrawn in view of Applicants arguments.

***35 USC § 103(a) rejections withdrawn***

The rejection of claims 9, 11, 12, 21-24 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klagsbrun et al in view of Singh et al is withdrawn in view of Applicants arguments.

**NEW REJECTIONS:**

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Art Unit: 1642

Claims 1, 9, 10, 12, 21-26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 1 12, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman*. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The claims are drawn to a method of determining disease status of a patient characterized by aberrant expression of a cell surface receptor complex wherein the receptor complex is VEGFR2 homodimers.

The specification describes disease status as the likelihood of contracting a disease, presence or absence of a disease, prognosis of disease severity and likelihood that a patient will respond to treatment by a particular therapeutic agent that acts through a receptor complex, wherein the disease is cancer or a disease characterized by aberrant angiogenesis, wherein the VEGF receptor complex is VEGFR1 homodimers.

The specification includes VEGFR2 homodimers in the definition of VEGF receptor (page 15 lines 10-22) and list the VEGFR2 homodimes as one of 33 exemplary receptor complexes (see Table I). The specification does not disclose any specific cancer or any disease characterized by aberrant angiogenesis associated with the expression of VEGFR2 homodimers.

Art Unit: 1642

Huss et al, (Cancer Res 61:2736-2743, 2001) describe VEGFR2 protein expression on high grade tumors but not in prostatic epithelial neoplasia or in well-differentiated or moderately differentiated lesions (see page 2741, column 1 1<sup>st</sup> paragraph to column 2 1<sup>st</sup> paragraph,). Thus VEGFR2 receptor expression was correlated with the transition from a differentiated to a poorly differentiated disease in a mouse prostate cancer model (Id). There was no discussion concerning VEGFR2 homodimer expression.

In addition, Huang et al (Int J Biochem Cell Bio 33:315-324, 2001) disclose that the binding of VEGF-A to VEGFR2 results in the homodimerization of VEGFR2 (see page 316, 1<sup>st</sup> column, 2<sup>nd</sup> paragraph,). Huang et al further disclose that signal transduction through VEGFR2 homodimers in transfected cell lines is distinct from VEGFR1 homodimers and VEGFR1 and VEGFR2 heterodimers (see Abstract).

Autiero et al (Nat Rev Med, 2003, 9:936-943) demonstrate that VEGFR1 and VEGFR2 form heterodimers spontaneously in mouse capillary endothelial cells (Figure 4a). Whitaker et al (JBC, 2001, 276:25520-25531) disclose that VEGFR2 and neuropilin-1 form a receptor complex in the absence of VEGF<sub>165</sub>. (Fig 5).

Tockman et al (Cancer Res., 1992, 52:2711s-2718s) teach considerations necessary in bringing a cancer biomarker to successful clinical application. Although the reference is drawn to biomarkers for early lung cancer detection, the basic principles taught are clearly applicable to other oncogenic disorders and associated markers such as CIN and HLA alleles and HPV type. Tockman et al teach that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials (see abstract). Early stage markers of carcinogenesis have clear biological plausibility as markers of preclinical cancer and if validated can be used for population screening (p. 2713s, col 1). The reference further teaches that once selected, the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed) cancer outcome. The essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in

Art Unit: 1642

advance of clinical cancer and *link* those marker results with subsequent histological confirmation of disease. This irrefutable link between antecedent marker and subsequent acknowledged disease is the essence of a valid intermediate end point marker (p. 2714, see Biomarker Validation against Acknowledged Disease End Points). Clearly, prior to the successful application of newly described markers, markers must be validated against acknowledged disease end points and the marker predictive value must be confirmed in prospective population trials (p. 2716s, col 2).

The art does not describe any correlation between the presence of VEGFR2 homodimers and cancer or a disease characterized by aberrant angiogenesis. Furthermore, the specification of the present invention does not disclose any correlation between the presence of VEGFR homodimers in a patient sample and the disease status of the patient. There are no examples in the specification concerning the correlation between the presence of VEGFR homodimers in a patient sample and the disease status of the patient.

Thus, given the vast number of potential diseases contemplated in the specification and the lack of any correlation between the presence of VEGFR homodimers in a patient sample and the disease status of the patient for any disease one could not predictably identify which disease would correlate with the presence of VEGFR2 homodimers with a reasonably expectation of success.

Applicants argue that the role of activated VEGFR2 in angiogenesis and cancer is well known as evidenced by Wedge et al and Rahimi.

Applicant's arguments have been fully considered but they are not persuasive. Rahimi disclose that VEGFR-1 is expressed by some carcinomas (page 1006 2<sup>nd</sup> column 3<sup>rd</sup> paragraph) and that receptor ligand interaction with the VEGFRs results in heterodimer and homodimer formation (page 1014, 1<sup>st</sup> column 2<sup>nd</sup> paragraph). Wedge discloses that binding of VEGF to VEGFR1 and VEGFR-2 induces receptor homodimerization and heterodimerization (page 4389, 2<sup>nd</sup> paragraph, 2<sup>nd</sup> paragraph). Neither Rahimi et al nor Wedge disclose that VEGFR2 homodimers are expressed specifically on tumor cells. Furthermore, the references cited by Applicants indicate

Art Unit: 1642

that homodimerization and heterodimerization of VEGFR-1 and VEGFR-2 receptors are characteristics of ligand binding to the VEGF receptors.

### ***Summary***

Claims 1, 9, 10, 12, 21-26 stand rejected

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Halvorson, PhD whose telephone number is (571) 272-6539. The examiner can normally be reached on Monday through Friday from 8:30am to 5 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley, can be reached at (571) 272-0898. The fax phone number for this Art Unit is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Mark Halvorson, PhD  
Patent Examiner  
571-272-6539

*Misook Yu*  
MISOOK YU  
PATENT EXAMINER  
~~YU~~  
PATENT EXAMINER  
PATENT EXAMINER